ORIGINAL ARTICLE

Effect of Bilastine Upon Nasal Obstruction

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Abstract

H_1 antihistamines constitute one of the main references for the treatment of allergic rhinitis. Classically, these drugs have been considered effective in controlling sneezing, rhinorrhea and itching, though they have not been regarded as particularly effective in application to nasal obstruction. The most recent studies, involving second-generation H_1 antihistamines (desloratadine, fexofenadine, levocetirizine, rupatadine), have shown these drugs to offer effects upon nasal obstruction significantly superior to those of placebo. The present review examines the effect of bilastine, a new, potent and highly specific H_1 antihistamine without sedative effects or cardiac toxicity, upon nasal obstruction. The analysis of the data from the different clinical trials indicates that in patients with allergic rhinitis, the effect of bilastine upon nasal obstruction is superior to that of placebo and similar to that of other second-generation H_1 antihistamines, manifesting within 24 hours after the start of treatment.

Key words: Bilastine. Nasal obstruction. Antihistamines. Allergic rhinitis.

Resumen

Los fármacos antihistamínicos H_1 constituyen uno de los pilares del tratamiento de la rinitis alérgica. Clásicamente, se ha considerado que resultan eficaces en el control de los estornudos, la rinorrea y el prurito, pero que no son demasiado eficaces sobre la obstrucción nasal. Los estudios más recientes, realizados con antihistamínicos H_1 de segunda generación (desloratadina, fexofenadina, levocetirizina, rupatadina), han mostrado que estos fármacos producen un efecto significativamente superior al del placebo sobre la obstrucción nasal. En la presente revisión se analiza el efecto de bilastina, un nuevo antihistamínico H_1, altamente específico, potente y desprovisto de efectos sedantes y de toxicidad cardiaca, sobre la obstrucción nasal. Del análisis de los datos procedentes de los distintos ensayos clínicos se concluye que, en los pacientes con rinitis alérgica, bilastina presenta un efecto sobre la obstrucción nasal superior al placebo y similar al de los otros antihistamínicos H_1 de segunda generación y que se manifiesta desde las 24 horas del inicio del tratamiento.

Palabras clave: Bilastina. Obstrucción nasal. Antihistamínicos. Rinitis alérgica.

Introduction

Allergic rhinitis is one of the most common chronic diseases in the world, affecting a variable percentage of the global population; the estimated prevalence is 10-25% [1], though in some cases the figure can reach 40% [2]. In Spain, different studies have evaluated the prevalence of allergic rhinitis, reporting figures between 11.7-21.5% [3-5]. In a study conducted in the Basque Country (Spain), Aizpiri et al. recorded a prevalence of pollen-induced allergic rhinitis of 10.6% [6]. In the recent ALERGOLOGICA 2005 study carried out in Spain, and involving a sample of 4991 patients seen in Spanish allergy clinics, 55% of the subjects were diagnosed with allergic rhinitis, representing therefore the most common diagnosis [7].

The characteristic manifestations of allergic rhinitis are nasal itching, sneezing salvoes, rhinorrhea and nasal obstruction (NO). NO is one of the symptoms causing most discomfort to patient. Thus, for example, in a study involving adolescents with seasonal allergic rhinitis, NO was present in almost 93% of the subjects, and was regarded as the most bothersome symptom [8]. In addition, patients with allergic rhinitis report a decrease in quality of life [9], due both to the inherent symptoms of rhinitis and to the physiopathology of the disorder, which can give rise to sleep disturbances [10,11]. Furthermore, some of the drugs used to treat rhinitis can have sedative effects [12]. These factors can have an impact upon occupational performance in adults [13], and on learning, in the case of children [14,15]. On the other hand, NO is particularly associated to sleep disturbances [16], and in patients with allergic rhinitis obstruction is three times more intense in decubitus than in the supine position [17]. Compared with healthy individuals without nasal disease, patients with rhinitis snore more often, suffer greater daytime drowsiness, and feel tired [18]. An added circumstance is the fact that antihistamines, particularly first-generation agents, can have a sedative effect [19]. Although it may be thought that such sedation induced by first-generation antihistamines could be of help in allowing such patients to fall asleep, it must be underscored that these drugs can cause daytime drowsiness, and moreover alter sleep structure – causing patients to feel that they have been unable to rest [20].

Since their market introduction, antihistamines have been the basis of treatment for allergic rhinitis. Traditionally, these drugs have been considered to be effective in providing relief from nasal itching, sneezing and rhinorrhea, but with little effect upon NO [21]. However, as it will be commented below, second-generation antihistamines have been reported to offer additional properties (reviewed in [22]) that could exert action upon the allergic inflammatory component.

Nasal Obstruction in Allergic Rhinitis

The nasal response to allergen provocation triggers all the characteristic symptoms of allergic rhinitis.

A first immediate response is observed, approximately 20 minutes after contact with the allergen, followed by a delayed response several hours later. The immediate response is particularly characterized by pruritus (itching), sneezing and rhinorrhea (runny nose), and it is mainly a consequence of mast cell degranulation. The mast cell mediators, including histamine and the cysteinyl leukotrienes, are able to cause the aforementioned symptoms [23,24]. In addition, the mast cells release chemokines and other chemotactic agents capable of attracting other cells to the inflammatory focus, including eosinophils. This in turn gives rise to the delayed phase of the allergic response, after 4-8 hours, and which basically constitutes a cellular response. The most characteristic feature of this late phase of allergic rhinitis is NO [25].

Histamine is a biogenic amine stored in the granules of the mast cells and basophils. It is released within a few seconds during IgE-mediated immediate hypersensitivity reactions. In this context, it has been shown that when performing nasal provocation with an allergen, histamine concentrations reach a peak within one minute after nasal provocation, and then drop drastically after 10 minutes [26]. Histamine is able to induce all the symptoms of allergic rhinitis, including NO, it is the most effective mediator of rhinorrhea, and practically the only mediator of sneezing [27]. Moreover, during the delayed response, a second peak in nasal levels of histamine is observed, accompanied by congestion and cellular inflammatory infiltration [28]. Histamine effects have also been described in this phase (reviewed in [29]), and which in sum comprise increased eosinophil chemotaxis, elevation of cytokines IL-1ß, IL-6, IL-4 and IL-5, increased VCAM-1 expression, and activation of the nuclear transcription factor NF-κB.

Antiinflammatory Effects of Antihistamines

H_1 antihistamines can act in different ways upon NO. On the one hand they logically counter the effects of histamine upon the H_1 receptor, and on the other hand they inhibit release of the mast cell and basophil mediators that contribute to development of the delayed phase of the allergic response [30]. In addition, however, and as it has been commented above, second-generation antihistamines have been reported to offer a number of antiinflammatory effects [22]. As an example, different antihistamines (cetirizine, loratadine and fexofenadine, among others) have been shown to regulate adhesion molecule expression [31]; rupatadine is able to reduce platelet aggregation factor production [32]; and mizolastine is able to inhibit leukotriene synthesis in vitro [22]. In sum, antihistamines appear to have additional antiallergic properties, apart from their action upon the H_1 histamine receptors. In this sense, it has been observed that some antihistamines are able to inhibit NF-κB [33]. However, this does not appear to represent a drug class effect, since such properties differ for each drug, and in any case its clinical relevance is not yet clear.

Properties of Bilastine

Bilastine is a new H_1 antihistamine chemically pertaining to the piperidine –benzimidazole subgroup, and which has been developed for the treatment of allergic rhinoconjunctivitis

(seasonal and perennial) and urticaria. Regarding the main characteristics of the drug (see [34, 35]), in brief, the molecule shows moderate-high affinity and important selectivity for the H_1 receptors. In the clinical setting, its effects manifest within 30-60 minutes, with a duration of 24 hours. Following absorption, bilastine is not metabolized and it is eliminated mainly in urine. The drug does not induce significant electrocardiographic changes at the doses studied, not even in the case of interaction with drugs that are known to increase its plasma concentration, such as ketoconazole. At therapeutic doses bilastine lacks sedative effects, it does not affect psychomotor performance or driving performance, and it does not interact with alcohol or lorazepam.

In the same way as other second-generation antihistamines, bilastine exerts antiinflammatory actions beyond its antihistaminic effects. Thus, in vitro studies involving a human mast cell line (HMC-1) and peripheral blood granulocytes have shown bilastine to be able to inhibit the spontaneous release of histamine IL-4 and TNF-α, as well as release induced by different stimuli – this representing a possible complementary mechanism of action [36].

Studies on the effect of bilastine upon nasal obstruction

In a recent review of the studies on the effect of some of the new second-generation antihistamines (levocetirizine, fexofenadine and desloratadine) upon NO, Bachert concluded that these drugs act upon NO in allergic rhinitis in a consistent and progressive manner over the course of treatment, and thus constitute adequate therapy for this symptom [37]. Rupatadine has also been found to act upon NO, as evidenced by acoustic rhinomanometry [38].

In the course of the clinical development of bilastine, different studies have been carried out involving over 4000 patients with seasonal allergic rhinitis, perennial allergic rhinitis or chronic urticaria. Some of them have evaluated the effect of the drug upon NO. Most of the available information, to which reference will be made later on, corresponds to filed data. The published studies are commented below.

Bachert et al. [39] evaluated the efficacy and safety of 20 mg of bilastine versus 5 mg of desloratadine and placebo in patients with seasonal allergic rhinitis. The study was carried out in several European countries and included a total of 849 patients, of which 721 were finally randomized. A significant reduction in the nasal symptoms scores was observed in both active drug groups versus placebo ($p<0.001$), manifesting from the first day and persisting for the full course of treatment. There were no statistically significant differences between bilastine and desloratadine.

Kuna et al. [40] analyzed 681 patients with seasonal allergic rhinitis administered with 20 mg of bilastine, 10 mg of cetirizine or placebo, on a randomized basis.

Table 1. Principal design characteristics of the clinical studies of bilastine used in the global analysis of nasal obstruction

Protocol	Weeks	Original title	Summary of evaluated symptoms
BILA 0401/RAE Phase II	2 weeks	*A double-blind, randomised, dose-ranging study in four parallel groups of 5, 10 and 20 mg Bilastine versus placebo for the treatment of seasonal allergic rhinitis*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes, ear and/or palatine itching
BILA 0501/RAP Phase II	4 weeks	*A double-blind, randomized, dose-ranging trial in four parallel groups of 10, 20 and 30 mg Bilastine versus placebo for the treatment of perennial allergic rhinitis*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes, ear and/or palatine itching
BILA 0701/RAE Phase II	2 weeks	*A dose-ranging placebo controlled parallel study of 2.5, 10, 20 and 40 mg bilastine for the treatment of seasonal allergic rhinitis*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes, ear and/or palatine itching
BILA 0802/RAE Phase III	2 weeks	*Double-blind, randomized, placebo controlled, Phase III study comparing the efficacy and safety of bilastine (20 mg and 40 mg once daily) and cetirizine 10 mg for the treatment of seasonal allergic rhinitis*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes, ear and/or palatine itching
BILA 1003/RAE Phase III	2 weeks	*Double-blind, randomized, placebo controlled, Phase III study comparing the efficacy and safety of bilastine 20 mg once daily and desloratadine 5 mg for the treatment of seasonal allergic rhinitis*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes, ear and/or palatine itching
BILA 1503/RAP Phase III	4 weeks	*A Phase III, comparative study for the efficacy and safety of Bilastine 20 mg versus Cetirizine 10 mg and Placebo in the treatment of perennial allergic rhinitis during 4 weeks, followed by a long-term safety extension with Bilastine 20 mg*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes
BILA 1704/RAE Phase III	2 weeks	*Double blind, randomised, placebo-controlled, Phase III study comparing the efficacy and safety of bilastine 20 mg once daily and Cetirizine 10 mg*	Nasal symptoms: rhinorrhea, sneezing, itching, obstruction Non-nasal symptoms: eye itching, tearing, red eyes

Table 2. Demographic data and baseline clinical characteristics of the patients included in the global analysis

		Bilastine 20 mg (n=1114)	Active comparators (n=923)	Placebo (n=1109)
Sex, n (%)	Female	606 (54.4)	522 (56.6)	628 (56.6)
	Male	508 (45.6)	401 (43.4)	481 (43.4)
Race, n (%)	Caucasian	997 (89.7)	841 (91.3)	1.002 (90.5)
	Negro	18 (1.6)	11 (1.2)	17 (1.5)
	Asian	49 (4.4)	26 (2.8)	40 (3.6)
	Other	48 (4.3)	43 (4.7)	48 (4.3)
	Not specified	2	2	2
Years from diagnosis, n (%)	< 5 years	358 (32.1)	305 (33.0)	373 (33.6)
	5-15 years	520 (46.7)	415 (45.0)	503 (45.4)
	> 15 years	236 (21.2)	203 (22.0)	233 (21.0)
Age (years)	Mean (SD)	31,60 (11.9)	31,69 (11.8)	31,14 (11.6)
VAS	Mean (SD)	71,1 (15.1)	72,3 (14.7)	71,6 (15.1)

Abbreviations: SD, standard deviation; VAS, visual analog scale.

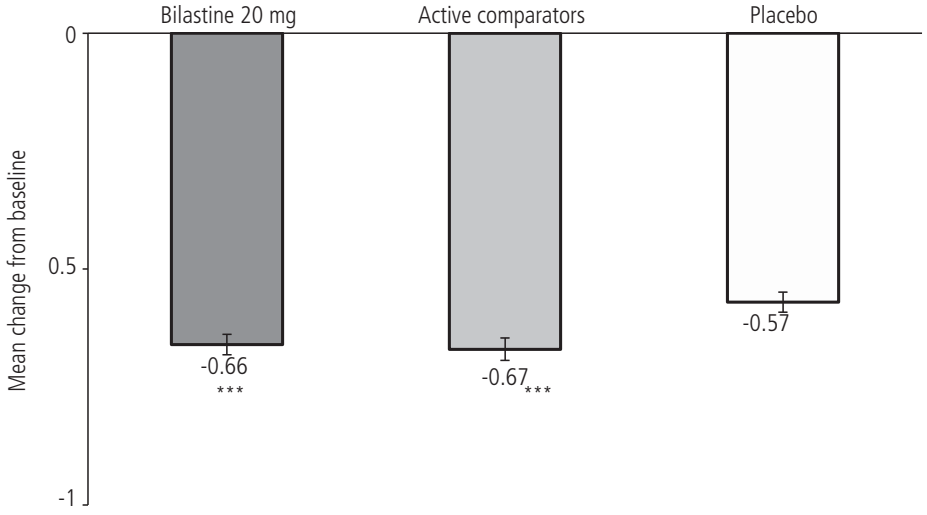

Figure 1. Mean change from baseline in nasal obstruction score (mean±SEM) during the observation period, in patients with seasonal allergic rhinitis treated for 14 days with bilastine 20 mg, placebo or another active comparator (desloratadine 5 mg and cetirizine 10 mg).
*** p<0,001 versus placebo.

Statistically significant improvement was also observed in nasal symptoms score in both active drug groups versus the placebo group (p<0.001). In the case of NO score, a statistically significant reduction versus placebo was observed (p <0.001) in both the bilastine group (-43.8% after 7 days and -48.5% after 14 days) and in the cetirizine group (-40.2% after 7 days and -50.6% after 14 days). There were no statistically significant differences between the two active drugs.

Provocation chamber studies

Horak et al. [41], in a Vienna provocation chamber study involving 75 patients with allergic rhinitis, found bilastine 20 mg, cetirizine 10 mg and fexofenadine 120 mg to reduce the symptoms more effectively than placebo (p<0.001), and with no significant differences among them. Bilastine showed rapid onset of action, one hour after administration, and in the same way as cetirizine and fexofenadine, maintained its

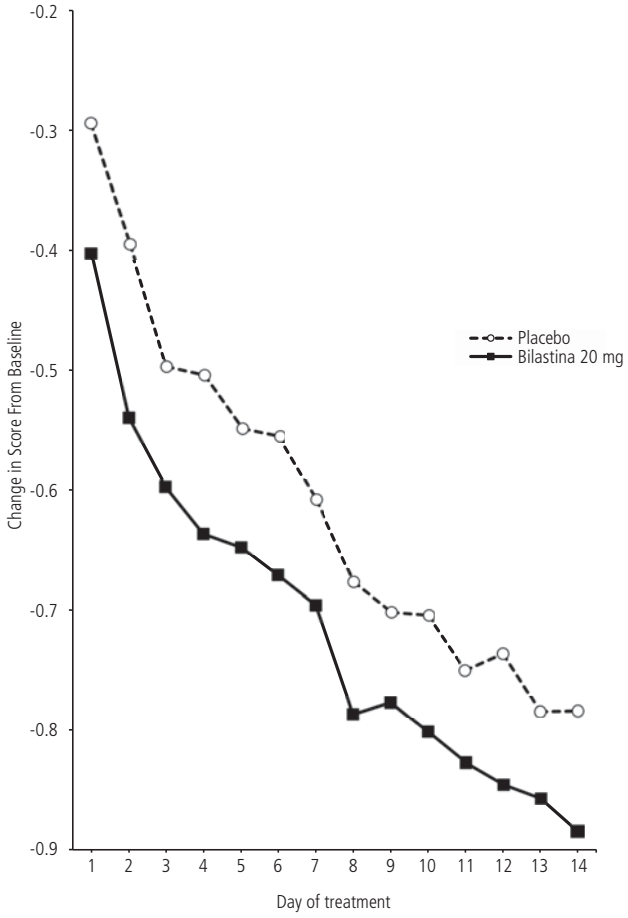

Figure 2. Effect of bilastine upon nasal obstruction during the observation period in the group of patients with seasonal allergic rhinitis. A significant difference versus placebo is observed ($p<0.05$) from the first day, and persisting for the full 14 days of treatment.

significant efficacy over a period of 26 hours. In the period between 22-26 hours, the efficacy of bilastine and cetirizine were significantly superior to that of fexofenadine. All three antihistamines showed a certain effect upon NO, as scored by the patients on a scale of 0-3, though not upon nasal flow as determined by rhinomanometry.

Global analysis of the data on nasal obstruction

The 7 clinical trials, phase II and phase III, in patients with seasonal allergic rhinitis and perennial allergic rhinitis comprised a total of 3846 subjects, of which 1814 received bilastine (at different doses), 1109 placebo, 681 cetirizine (10 mg), and 242 desloratadine (5 mg). Table 1 describes the characteristics of the analyzed studies.

The global analysis of phase II and III trials in patients with seasonal allergic rhinitis and perennial allergic rhinitis, involving different doses of bilastine and two different comparator drugs, logically implies a certain heterogeneity, and therefore, for the purposes of the statistical analysis, the following premises were considered: (i) only the data corresponding to the 20 mg dose of bilastine were used (n=1114), this being the dose selected as the therapeutic dose; (ii) the data corresponding to the two active comparator drugs were jointly analyzed (n=923); and (iii) due to the different duration of the studies, the recommendations of the *Clinical Development Programs for Drug Products* of the United States FDA [42] were followed, using as variable for the statistical analysis the change of the mean from baseline over the course of the observation period.

Taking the above premises into account, the resulting population presented homogeneous demographic characteristics among the three groups, with a predominance of females in all three groups, and a great majority of Caucasians (Table 2).

The global analysis of the data relating to NO symptom as evaluated by the patients showed placebo to induce a mean reduction from baseline of -0.57 points, while bilastine 20 mg induced a reduction of -0.66 points ($p<0.001$ versus placebo), and the active comparators induced a reduction of -0.67 points ($p<0.001$ versus placebo) – no statistically significant differences were observed between the two active drug groups (Figure 1).

A separate analysis was also performed on the effect of bilastine upon NO in the clinical trials involving patients with seasonal allergic rhinitis. In this context, the score for NO was found to be significantly lower in the bilastine-treated group than in that of placebo from the first day of treatment ($p<0.05$), and in general terms this effect was maintained throughout the period of observation (Figure 2).

Conclusion

H_1 antihistamines constitute first-line treatment for allergic rhinitis. These drugs classically have been considered to act upon itching, sneezing and rhinorrhea. There is a growing body of evidence that H_1 antihistamines are effective in application to NO, and this has also been supported by the analyzed clinical trials in reference to bilastine. This effect could be related to antiallergic and antiinflammatory actions beyond the activity of these drugs upon H_1 receptors, though the effect varies among the different molecules, and its clinical relevance remains unclear. In this sense, bilastine, a new and potent H_1 antihistamine administered in a single daily dose and lacking cardiac and central nervous system effects, has been shown to offer efficacy in application to allergic rhinitis, with a significant effect upon NO.

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Conflicts of interest

Joan Bartra Tomás with: UCB, MSD, Dr. Esteve, GSK,

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